[Chem. Pharm. Bull. 27(9)2229—2232(1979)]

UDC 547.682.1.04 : 547.655.6.04

Synthesis of Polycyclines. II.[1] Synthesis of 12-Hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenones

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(Received March 7, 1979)

A convenient synthesis is reported of 1-substituted 7,8,9,10-tetrahydro-5,12-naphthacenediones (**3a**—**d**) and 4-substituted 12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenones (**4a**—**c**) by means of the Diels-Alder reaction of 1,4-naphthoquinones (**1a**—**d**) with 1,2-dimethylenecyclohexane, followed by aromatization through dehydrogenation (**3a**—**d**) or by catalytic hydrogenation (**4a**—**c**).

Keywords——5a,6,7,8,9,10,11,11a-octahydro-5,12-naphthacenediones; 7,8,9,10-tetrahydro-5,12-naphthacenediones; 12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenones; Diels-Alder reaction; aromatization; catalytic hydrogenation

In connection with synthetic studies on anthracyclic compounds having antitumor activity, we have developed a simple synthetic route to 12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenones (**4a**—**c**) using the Diels-Alder reaction. This paper describes the synthesis of these anthracyclines, together with some 7,8,9,10-tetrahydro-5,12-naphthacenediones (**3a**—**d**).

The starting materials, 5-substituted-1,4-naphthoquinones (**1a**—**d**), used as dienophilic components, were synthesized from 1,4-naphthoquinone or 1,5-dihydroxynaphthaline by the published methods.[3] 1,2-Dimethylenecyclohexane, used as a dienic component, was obtained by the method of Bailey *et al.*[4]

The Diels-Alder reaction of 5-substituted-1,4-naphthoquinones (**1a**—**d**) with 1,2-dimethylenecyclohexane in alcoholic solution gave the corresponding adducts; 5a,6,7,8,9,10,11,11a-octahydro-5,12-naphthacenedione (**2a**), its 1-hydroxy compound (**2b**), the 1-methoxy compound (**2c**), and the 1-nitro compound (**2d**) in good yields. The nuclear magnetic resonance (NMR) spectra of 2a—c showed 5a-H and 11a-H methine protons at δ 3.30±0.30 as multiplets.

The Diels-Alder adducts (**2a**—**d**) were aromatized by air oxidation in alcoholic sodium hydroxide. The adducts (**2a**—**d**) lost 2 moles of hydrogen to aromatize the A or B ring. The ultraviolet (UV) spectra of the aromatized compounds (3a—**d**) showed benzenoid and quinonoid absorption maxima shifted to the longer wave region compared to the corresponding adducts (**2a**—**d**), as shown in Table I, and exhibited features characteristic of 9,10-anthraquinone derivatives.[5] This indicates that the aromatization occurred at the B ring. The NMR signals of 7-H and 10-H protons of **3a**—**d** were shifted downfield 0.82—1.07 ppm from those of the corresponding **2a**—**d**, presumably due to the effects of the ring current of the adjacent aromatic B ring. Similarly, the signals of 8-H and 9-H protons of **3a**—**d** were shifted downfield 0.02—0.27 ppm from those of the corresponding **2a**—**d**.

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1) Part I: N. Oda, K. Kobayashi, T. Ueda, and I. Ito, *Chem. Pharm. Bull.* (Tokyo), **26**, 2578 (1978).
2) Location: *3-1 Tanabe-dori, Mizuho-ku, Nagoya 467, Japan.*
3) *a*) C. Grundmann, *Synthesis*, **1977**, 644; *b*) R.G. Jesaitis, and A. Krantz, *J. Chem. Educ.*, **49**, 436 (1971); *c*) J.F. Garden and R.H. Thomson, *J. Chem. Soc.*, **1957**, 2483; *d*) S. Galinowsky, Ger. Patent 1247288 (1967) [(*C.A.*, **68**, 70179*t* (1968)].
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2a was hydrogenated in the presence of palladium charcoal. The theoretical amount (1 mol) of hydrogen was absorbed in 5 min to give 12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (**4a**).

2b was hydrogenated in the same manner over palladium charcoal to give 4,12-dihydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (**4b**). The infrared (IR) spectrum showed a hydrogen-bonded carbonyl band at 1638 cm^{-1}, and a hydrogen-bonded aromatic hydroxyl resonance at δ 12.45 in the NMR spectrum. **4b** was acetylated with acetic anhydride to give the 4,12-diacetoxy compound (**5a**). The 12-H proton of **5a** showed a downfield shift of 1.27 ppm in comparison with the 12-H proton of **4b**.

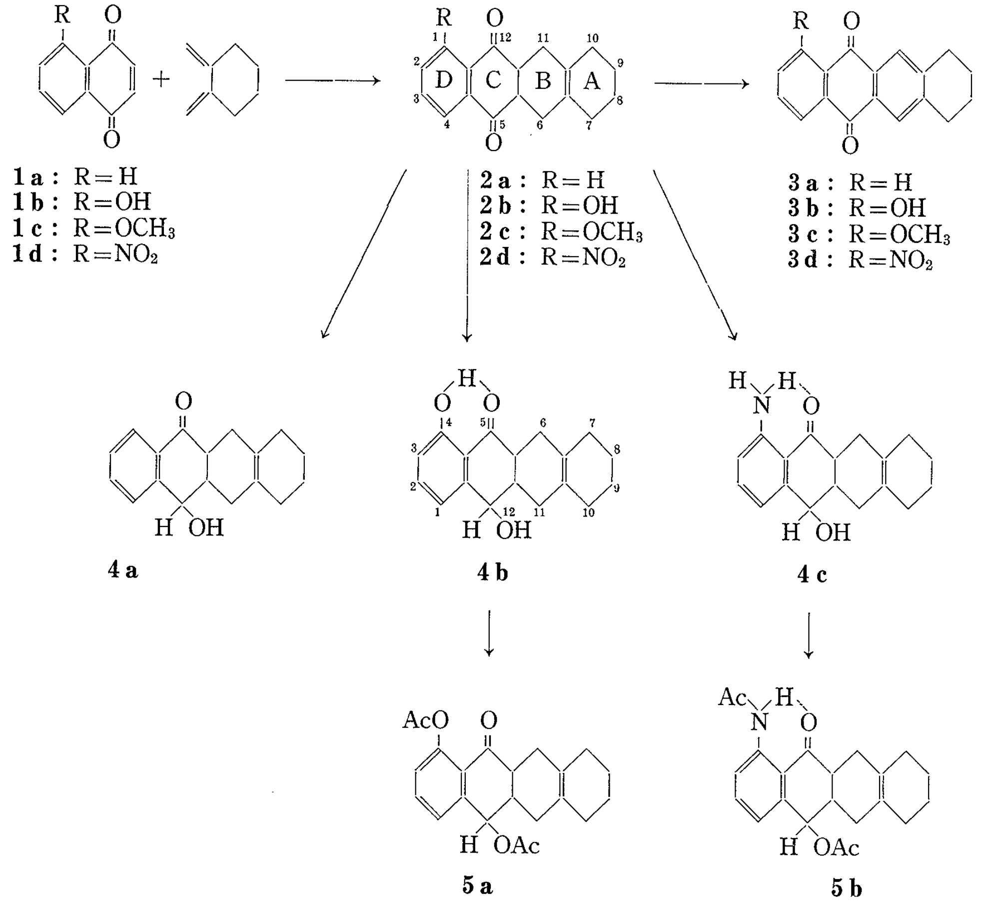


Chart 1

Table I. UV Data for 5a,6,7,8,9,10,11,11a-Octahydro-5,12-naphthacenediones (**2a**—**d**) and 7,8,9,10-Tetrahydro-5,12-naphthacenediones (**3a**—**d**)

	$\lambda_{max}^{ethanol}$ nm (log ε)			
2a		223(4.52)	250(4.06)	305(3.30)
2b	210(4.15)	228(4.25)	264(3.83)	347(3.64)
2c	207(4.16)	227(4.44)	260(sh)	336(3.79)
2d		220(4.33)	267(4.05)	330(3.06)
3a	211(4.33)		263(4.65)	330(3.68)
3b	217(4.58)		268(4.61)	400(3.83)
3c	215(4.51)		265(4.63)	376(3.78)
3d	213(4.58)	236(4.48)	269(4.79)	336(3.91)

sh: shoulder.

2d was hydrogenated in the same way as **2a**, **b**, and 4 mol of hydrogen was absorbed in 1 hr to give 4-amino-12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (**4c**). The IR spectrum showed a carbonyl band hydrogen-bonded with amine at 1645 cm^{-1} for the 5-carbonyl. **4c** was acetylated with acetic anhydride to give the 4-acetamino-12-acetoxy compound (**5b**). The 12-H proton of **5b** showed a downfield shift of 1.40 ppm in comparison with that of **4c**.

Experimental

Melting points were measured on a Mettler FP-61 melting point apparatus and are uncorrected. UV spectra were measured on a Shimadzu UV-210A double-beam spectrophotometer. IR spectra were taken on a Nihon Bunko IR-G spectrophotometer. NMR spectra were recorded on a Jeol JNM-NH 100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were determined with a Hitachi M-52 mass spectrometer.

General Procedure for 5a,6,7,8,9,10,11,11a-Octahydro-5,12-naphthacenediones (**2a**—**d**)——A mixture of 0.1 mol of 5-substituted 1,4-naphthoquinone (**1a**—**d**)[3] and 0.12 mol of 1,2-dimethylenecyclohexane[4] in 1000 ml of alcohol was refluxed for 4 hr under nitrogen. After cooling, the crystals which appeared were filtered off. The filtrate was condensed to give a second crop of crystals. The combined crystals were recrystallized from alcohol or ethyl acetate to give colorless needles. The physical and analytical data for these compounds are listed in Table II, and the spectral data are listed in Table III.

Table II. Physical and Analytical Data for 5a, 6,7,8,9,10,11,11a-Octahydro-5,12-naphthacenediones (**2a**—**d**)

	Appearance	mp (°C)	Yield (%)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
2a	Colorless needles	161—162	90.3	$C_{18}H_{18}O_2$	81.17	6.81		80.99	6.61	
2b	Colorless needles	175—176	87.4	$C_{18}H_{18}O_3$	76.57	6.43		76.52	6.50	
2c	Colorless needles	143—144	96.3	$C_{19}H_{20}O_3$	77.00	6.80		77.12	6.90	
2d	Colorless needles	200—203	97.6	$C_{18}H_{17}NO_4$	69.44	5.50	4.50	69.11	5.39	4.47

Table III. Spectral Data for 5a,6,7,8,9,10,11,11a-Octahydro-5,12-naphthacenediones (**2a**—**d**)

	IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	NMR ($CDCl_3$) δ	MS *m/e* (M^+)
2a	2906, 2856 (C-H) 1687 (C=O)	1.60 (4H, m, 8,9H), 1.88 (4H, m, 7,10H), 2.10—2.50 (4H, m, 6,11H), 3.28—3.43 (2H, m, 5a,11aH)	266
2b	2916, 2880 (C-H), 1701 (C=O), 1642 (C=O hydrogen bonded)	1.60 (4H, m, 8,9H), 1.89 (4H, m, 7,10H), 2.15—2.60 (4H, m, 6,11H), 3.35 (2H, m, 5a,11aH)	282
2c	2845 (C-H), 1691 (C=O)	1.59 (4H, m, 8,9H), 1.87 (4H, m, 7,10H), 2.10—2.48 (4H, m, 6,11H), 3.29—3.40 (2H, m, 5a,11aH), 3.96 (3H, s, CH_3O)	296
2d	2916, 2876 (C-H), 1700 (C=O), 1530, 1370 (NO_2)	1.60 (4H, m, 8,9H), 1.88 (4H, m, 7,10H), 2.12—2.55 (4H, m, 6,11H), 3.30—3.60 (2H, m, 5a,11aH)	311

Aromatization of 5a,6,7,8,9,10,11,11a-Octahydro-5,12-naphthacenediones (**2a**—**d**)——Air was bubbled through a solution of 4 g of the octahydro compound (**2a**—**d**) in 600 ml of alcoholic 0.4% NaOH for 4—10 hr until the original dark-red or geen color disappearred. The precipitate was collected and crystallized from alcohol or benzene to give the product. The physical and analytical data for these compounds are listed in Table IV, and the spectral data are listed in Table V.

12-Hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (**4a**)——A solution of 1.33 g of **2a** in 250 ml of EtOH was hydrogenated over 0.1 g of 5% palladium charcoal for 10 min at room temperature, during which time 120 ml (1.07 mol) of hydrogen was absorbed. The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from benzene to give 1.26 g (94%) of colorless needles, mp 190—191°. *Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.56;

Table IV. Physical and Analytical Data for 7,8,9,10-Tetrahydro-5,12-naphthacenediones (**3a**—**d**)

	Appearance	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	Light yellow needles	218—219	81.2	$C_{18}H_{14}O_2$	82.42	5.38		82.41	5.32	
3b	Light yellow needles	202—204	81.1	$C_{18}H_{14}O_3$	77.68	5.07		77.67	5.09	
3c	Yellow needles	180	65.9	$C_{19}H_{16}O_3$	78.01	5.52		78.25	5.23	
3d	Yellow plates	258—259	54.7	$C_{18}H_{13}NO_4$	70.35	4.26	4.56	70.33	4.17	4.39

Table V. Spectral Data for 7,8,9,10-Tetrahydro-5,12-naphthacenediones (**3a**—**d**)

	IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	NMR ($CDCl_3$) δ	MS *m/e* (M^+)
3a	2906, 2826 (C-H), 1674 (C=O),	1.82—1.92 (4H, m, 8,9H), 2.89—3.00 (4H, m, 7,10H)	262
3b	2915, 2836 (C-H), 1660 (C=O), 1630 (C=O hydrogen bonded)	1.72—1.90 (4H, m, 8,9H), 2.75—2.80 (4H, m, 7,10H) 12.50 (1H, s, OH)$^{a)}$	278
3c	2936, 2846 (C-H), 1665 (C=O),	1.80—1.87 (4H, m, 8,9H), 2.84—3.00 (4H, m, 7,10H), 4.01 (3H, s, CH_3O)	292
3d	2935, 2856 (C-H), 1668 (C=O), 1531, 1330 (NO_2)	1.53—1.65 (4H, m, 8,9H), 2.58—2.73 (4H, m, 7,10H)$^{b)}$	307

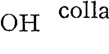
a) Disappeared upon addition of D_2O.
b) In pyridine-d_5.

H, 7.52. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3406 (OH), 1699 (C=O). NMR ($CDCl_3$) δ: 2.38 (1H, s, OH), 5.27 (1H, d,  collapsed to a singlet on irradiation at δ 2.74—2.96 (5a, 11a-H)). MS *m/e*: 268 (M^+).

4,12-Dihydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (4b)——A solution of 3.0 g of **2b** in 400 ml of EtOH was hydrogenated over 0.2 g of 5% palladium charcoal for 25 min at room temperature, during which time 250 ml (1.05 mol) of hydrogen was absorbed. The mixture was treated in the same manner as for **4a** to give 2.7 g (97.0%) of colorless needles, mp 209—210°. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.04; H, 7.30. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3406, 3326 (OH), 1638 (C=O hydrogen-bonded). NMR ($CDCl_3$) δ: 5.10 (1H, d,  collapsed to a singlet on irradiation at 2.97—3.02 (5a, 11a-H), 5.18 (1H, m, 12-OH disappeared upon addition of D_2O), 12.45 (1H, s, aromatic OH). MS *m/e*: 284 (M^+).

4-Amino-12-hydroxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (4c)——A solution of 1.56 g of **2d** in 300 ml of EtOH was hydrogenated over 0.2 g of 5% palladium charcoal for 1 hr at room temperature, during which time 458 ml (4.08 mol) of hydrogen was absorbed. The mixture was treated in the same manner as for **4a** to give 1.2 g (84.5%) of colorles sneedles, mp 234—235°. *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.36; H, 7.56; N, 4.91. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3486, 3336 (NH_2), 1645 (C=O hydrogen-bonded). NMR ($CDCl_3$) δ: around 4.40 (2H, very br. m, NH_2 disappeared upon addition of D_2O). 4.98 (1H, d,  collapsed to a singlet on irradiation at 2.52—2.87 (5a, 11a-H)). MS *m/e*: 283 (M^+).

4,12-Diacetoxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (5a)——A mixture of 1 g of **4b**, 10 ml of pyridine, and 5 ml of Ac_2O was allowed to stand overnight, then the solvent was evaporated to dryness under reduced pressure. The residue was crystallized from EtOH to give 0.97 g (74.9%) of colorless prisms, mp 140—141°. *Anal.* Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.78; H, 6.51. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1779, 1752 (CH_3CO), 1702 (C=O). NMR ($CDCl_3$) δ: 2.21 (3H, s, 12-CH_3CO), 2.35 (3H, s, 4-CH_3CO), 6.37 (1H, d,  collapsed to a singlet on irradiation at 2.76—2.96 (5a, 11a-H). MS *m/e*: 368 (M^+).

4-Acetamino-12-acetoxy-5a,6,7,8,9,10,11,11a-octahydro-5(12*H*)-naphthacenone (5c)——A mixture of 0.6 g of **4c**, 6 ml of pyridine, and 3 ml of Ac_2O was allowed to stand overnight. The mixture was treated in the same manner as for **5a** to give 0.6 g (77.1%) of colorless prisms, mp 138—139°. *Anal.* Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.82; H, 6.76; N, 3.65. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3247 (NH), 1755, 1721 (CH_3CO), 1655 (C=O). NMR ($CDCl_3$) δ: 2.25 (6H, m, 2 CH_3CO), 6.38 (1H, d,  collapsed to a singlet on irradiation at 2.80—3.04 (5a, 11a-H)). MS *m/e*: 367 (M^+).

Acknowledgement The authors are indebted to the staff of the Microanalytical Center of this Faculty for elemental analyses and NMR spectral measurements.